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Glaxo Smith Kline
c/o The Nath Law Group
112 South West St.
Alexandria, VA 22314-2825

EXAMINER	
ANDERSON, JAMES D	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/617,350
Filing Date: July 11, 2003
Appellant(s): NAMBURI ET AL.

Joshua B. Goldberg
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 6/2/2010 appealing from the Office action mailed 6/12/2009.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

1-7, 15-20, 22-23, and 42

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

Gillis et al. WO/00/03697 (Published Jan. 27, 2000)

Ishibashi et al. US Patent Application Publication No. 2003/0012815 A1; Published Jan. 16, 2003; Filed Jan. 26, 2001

Lynenskjold et al. US Patent Application Publication No. 2003/0211168; Published Nov. 13, 2003; Filed Feb. 19, 2001

6,245,351	Nara et al.	06-2001
6,497,905	Vladyka et al.	12-2002

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 23 is rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over **Gilis *et al.*** (WO 00/03697; Published Jan. 27, 2000).

Instant claim 23 recites a pharmaceutically acceptable particle produced by the process of claim 1.

Applicant's attention is directed to MPEP 2113, which discusses the patentability of product-by-process claims. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

Gilis *et al.* teach pharmaceutically acceptable particles comprising a water-insoluble azole antifungal agent and a water-soluble polymer coated onto core particles (page 14, lines 6-12; Example at pages 14-16; claims 1-6). Gilis *et al.* teach residual dichloromethane content of less than 600 ppm, preferably less than 250 ppm, which reasonably meets the limitation "..said oral dosage form is essentially free of methylene chloride" (page 4, lines 24-32; claims 1-6).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 15-16, 18-20, 22-23, and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Gilis *et al.*** (WO 00/03697; Published Jan. 27, 2000) and **Ishibashi *et al.*** (U.S. Patent Application Publication No. US 2003/0012815 A1; Published Jan. 16, 2003; Filed Jan. 26, 2001) in view of **Lynenskjold *et al.*** (US 2003/0211168 A1; Published Nov. 13, 2003; Filed Feb. 19, 2001) and **Nara *et al.*** (USP No. 6,245,351 B1; Issued Jun. 12, 2001; Filed Mar. 4, 1997), each already of record, for the reasons set forth at pages 8-12 of the previous Office Action dated 12/4/2008, of which said reasons are herein incorporated by reference.

Claimed Invention

The claims recite a method of manufacturing a water-insoluble azole antifungal agent oral dosage form comprising the steps of:

1) providing a single phase working solution comprising a) a water-insoluble azole antifungal agent; b) water; c) a water-soluble polymer, and d) a solvent selected from the group consisting of alcohol, acetone, and mixtures thereof;

2) providing core particles formed from a pharmaceutically acceptable material;

3) combining said working solution with said particles to produce water-insoluble azole antifungal agent-coated particles;

4) drying said water-insoluble azole antifungal agent-coated particles; and

5) forming said dried particles into an oral dosage form,

wherein said working solution is essentially free of methylene chloride, and said oral dosage form is essentially free of methylene chloride.

Teachings of Gilis et al.

Gilis et al. teach pellets having a core coated with an antifungal and a polymer (Abstract). With respect to solvents used in forming coated core particles, the reference discloses that dichloromethane and methanol are both Class 2 solvents whose presence in pharmaceutical products should be limited (page 2, lines 28-30). Specifically, the pellets disclosed in Gilis *et al.* comprise: a) a central, rounded or spherical core having a diameter of about 710-1190 μM); b) a coating film of a **water-soluble polymer** and an **antifungal agent**; and c) a seal-coating polymer layer, characterized in that the residual solvent levels in said pellets is within limits set by the ICH, that is, the concentration of dichloromethane is less than 600 ppm, most preferably less than 250 ppm (page 4, lines 24-32). Accordingly, Gilis *et al.* disclose using ethanol as an alcoholic co-solvent that is necessary for applying the drug coat layer to the cores (page 4, lines 34-35), thus meeting the limitations of claim 15. Water-soluble polymers include those recited in instant claim 16, for example, hydroxypropyl methylcellulose, polyvinylpyrrolidones and methacrylates (page 6, line 23 to page 7, line 3). Such polymers are disclosed to have an apparent viscosity of 1 to 100 mPas when dissolved in a 2% aqueous solution, thus reasonably encompassing the limitations of instant claim 4 (page 5, lines 32-34). With respect to the

composition of the core particles recited in instant claims 18-19, Gilis *et al.* disclose identical core particles composed of, for example, mannitol or microcrystalline cellulose (page 5, lines 8-19). Preferred antifungal agents for use as drugs in the drug-coating layer are lipophilic azole antifungals, in particular itraconazole (page 7, lines 10-11). The instantly claimed weight ratio of active agent to polymer is obviated by those disclosed at page 7, lines 15-30, for example, 1:1 to 1:5. With respect to the limitations of instant claim 22 wherein an external coating is applied to the drug coated spheres, Gilis *et al.* disclose such an external coating at page 8, lines 28-32. The addition of surfactants as recited in instant claim 3 is disclosed at page 9, lines 1-4. A drying step as recited in claim 1 is disclosed at page 10, lines 32-38).

The reference thus clearly suggests a process of forming drug-coated particles comprising the same steps as those instantly claimed. For example, at page 9, lines 14 to page 11, line 27, Gilis et al. describes a method of preparing coated pellets comprising the steps of: 1) preparing a drug coating solution by dissolving into a "suitable solvent system" appropriate amounts of an antifungal agent and a water-soluble polymer, wherein the solvent system comprises a mixture of methylene chloride and an alcohol, preferably ethanol; 2) providing core particles formed from a pharmaceutically acceptable material; 3) combining said drug coating solution with said particles to produce antifungal agent-coated particles; 4) drying said antifungal agent-coated particles; and 5) forming said dried particles into an oral dosage form. Further, Gilis *et al.* suggest that the dichloromethane content of the coating should be limited, such as by drying in a microwave. Gilis *et al.* differ from the claims **only** with respect to the solvent used in the coating solution. Whereas Gilis et al. used a solvent comprising a water-soluble polymer, methylene chloride, and an alcohol, the instant claims recite a solvent comprising a water-soluble polymer, water, and alcohol, acetone, or mixtures thereof.

Teachings of Ishibashi et al.

Ishibashi *et al.* disclose drug-containing core substances having a multi-layered coating layer (Abstract). With respect to the coating solution used to coat the disclosed core particles, the reference discloses that the solvent system should dissolve both the hydrophobic organic compound and water-soluble polymer (page 6, ¶ [0057]). Suitable solvents include alcohols such as ethanol as well as ketones such as acetone (*id.*). The reference thus teaches that ethanol

and acetone are suitable solvents for applying a coating solution to a core particle. The reference does not teach coating solutions additionally comprising water as instantly claimed.

Teachings of Lynenskjold et al.

Lynenskjold *et al.* teach a process for the production of drug carrier pellets comprising spray-drying a solution of a physiologically tolerable cellulosic binder containing an active drug (Abstract; Example 5). With respect to active drug substances coated onto the spray-dried pellets, the inventors teach that the antifungal, ketoconazole, as recited in claim 42, is one such active drug substance (page 4, [0046]). The active drug substance will generally be applied to the spray-dried pellets in the form of a solution or dispersion in a physiologically tolerable solvent or solvent mixture, optionally incorporating other components such as binders, sweeteners, pH modifiers, antioxidants, etc. (page 4, [0050]). The coatings may also include further components, including antiadhesives, which are reasonably interpreted as surfactants as recited in claims 3 and 17 (page 5, [0057]). With respect to the coating solutions, while the use of aqueous solutions or dispersions is preferred, organic solvents such as ethanol and acetone as recited in the instant claims may also be used (page 5, [0058]). Methylene chloride, as taught in Gilis *et al.* cited *supra*, may be used but is generally not preferred (*id.*).

Teachings of Nara et al.

Nara *et al.* teach solvents for coating solutions may be water, an organic solvent, or mixtures thereof (col. 6, lines 34-35). The organic solvent may be any organic solvent capable of dissolving a water-insoluble substance, such as ethanol or acetone as recited in the instant claims (col. 6, lines 38-46). Water and its mixture with an organic solvent are "preferably used as solvent of coating composition" (col. 6, lines 47-48).

Analysis and Examiner's Determination of Obviousness

The above cited references continue to render the instant claims obvious because optimization of coating solutions for applying drugs to core particles is clearly a matter of routinely testing different solvent mixtures for optimal dissolution of active agent. The fact that Applicants use water instead of methylene chloride as disclosed in Gilis *et al.* does not render in

the instant claims patentable in view of the fact that Ishibashi, Lynenskjold, and Nara all teach, suggest, and motivate the use of solvents other than containing methylene chloride for coating core particles, and Gilis et al. explicitly teaches that the methylene chloride content of the coated particles should be minimized. As such, one skilled in the art would immediately see the benefit of using a coating solution that omits methylene chloride, such as a coating solution comprising water, a water-soluble polymer, and a solvent selected from an alcohol, acetone, and mixtures thereof as motivated by the cited prior art.

Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Gilis *et al.*** (WO 00/03697; Published Jan. 27, 2000), **Ishibashi *et al.*** (U.S. Patent Application Publication No. US 2003/0012815 A1; Published Jan. 16, 2003; Filed Jan. 26, 2001), **Lynenskjold *et al.*** (US 2003/0211168 A1; Published Nov. 13, 2003; Filed Feb. 19, 2001), and ***Nara et al.*** (USP No. 6,245,351 B1; Issued Jun. 12, 2001; Filed Mar. 4, 1997) as applied to claims 1-6, 15-16, 18-20, 22-23, and 42 above, and further in view of **Vladyka *et al.*** (USP No. 6,497,905 B1; Issued Dec. 24, 2002; Filed Mar. 20, 2000), each already of record, for the reasons set forth at page 12 of the previous Office Action dated 12/4/2008, of which said reasons are herein incorporated by reference.

Gilis *et al.*, Ishibashi *et al.*, Lynenskjold *et al.*, and Nara *et al.* teach as applied *supra* and are here applied to claim 7 in the same manner. The references do not teach the amorphous form of an azole antifungal agent as recited in claim 7.

However, Vladyka *et al.* teach that members of the class of azole antifungal agents such as ketoconazole and itraconazole have very low solubility in aqueous media and will benefit from the method of conversion to the amorphous state (col. 5, lines 36-43).

Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to provide the claimed azole antifungal agent in the amorphous state because Vladyka et al. teach that these agents having low aqueous solubility will benefit from providing them in their amorphous state. The skilled artisan would reasonably expect that an azole antifungal agent in its amorphous state will exhibit increased solubility (Vladyka et al., col.

5, lines 20-25) in the aqueous coating solutions as motivated and suggested by Gilis *et al.*, Ishibashi *et al.*, Lynenskjold *et al.*, and Nara *et al.* as discussed *supra*.

Claim 17 remains rejected under 35 U.S.C. 103(a) as being unpatentable over **Gilis *et al.*** (WO 00/03697; Published Jan. 27, 2000), **Ishibashi *et al.*** (U.S. Patent Application Publication No. US 2003/0012815 A1; Published Jan. 16, 2003; Filed Jan. 26, 2001), **Lynenskjold *et al.*** (US 2003/0211168 A1; Published Nov. 13, 2003; Filed Feb. 19, 2001), and **Nara *et al.*** (USP No. 6,245,351 B1; Issued Jun. 12, 2001; Filed Mar. 4, 1997) as applied to claims 1-6, 15-16, 18-20, 22-23, and 42 above, and further in view of **Martindale: The Complete Drug Reference** (Pharmaceutical Press, London, 2002, pages 1344-1349), each already of record, for the reasons set forth at page 13 of the previous Office Action dated 12/4/2008, of which said reasons are herein incorporated by reference.

Gilis *et al.*, Ishibashi *et al.*, Lynenskjold *et al.*, and Nara *et al.* teach as applied *supra* and are here applied to claim 17 in the same manner. The references do not teach the specific surfactants as recited in claim 17.

However, Martindale teaches that surfactants are compounds that can reduce the interfacial tension between two immiscible phases (page 1344), specifically teaching that polysorbates (20, 40, 60, and 80), polyoxyl castor oils, poloxamers, and sorbitan esters (*e.g.*, sorbitan laureate, sorbitan palmitate, and sorbitan stearate) are suitable for use as surfactants in the manufacture of pharmaceuticals (pages 1346-1349).

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use any known surfactant, such as those taught by Martindale, in the manufacture of azole antifungal-coated particles. Gilis *et al.* teach that surfactants can be incorporated in pharmaceutical preparations comprising azole antifungal agents. As such, the skilled artisan would have been imbued with at least a reasonable expectation that the surfactants taught in Martindale would be amiable for use in the coating methods suggested and motivated by the cited references.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-7, 15-20, 22-23, and 42 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 6,663,897. Although the conflicting claims are not identical, they are not patentably distinct from each other because the presently examined application claims are anticipated by or would have been obvious over the methods of manufacturing an itraconazole oral dosage form that is substantially free of residual methylene chloride as recited in the '897 patent claims. While the claims of the '897 patent recite a working solution additionally comprising a strong acid, the instant claims do not exclude the presence of a strong acid in the working solution. Furthermore, while the claims of the '897 patent are limited to particles comprising itraconazole, it would have been obvious to one skilled in the art at the time the invention was made that the methods of the '897 patent would also be effective in forming oral dosage forms comprising other water-insoluble antifungal agents such as ketoconazole as recited in instant claim 42.

(10) Response to Argument

Applicant's arguments filed 6/2/2010 have been fully considered but they are not persuasive.

Firstly, it is noted that Appellants present no arguments in traverse of the 35 U.S.C. 103 rejection of claim 17 as being unpatentable over Gilis *et al.*, Ishibashi *et al.*, Lynenskjold *et al.*, and Nara *et al.* in view of Martindale or the Obviousness-Type Double Patenting rejection of claims 1-7, 15-20, 22-23, and 42 as being unpatentable over claims 1-17 of USP No. 6,663,897. Accordingly, the Examiner presumes that Appellants agree with these grounds of rejection.

With regard to the rejection of claim 23 under 35 USC 102(b) or 103(a), Appellants argue that Gillis *et al.* fail to teach or suggest all of the limitations of the claim. In this regard, Appellants argue that since the working solution of claim 1 is "essentially free of methylene chloride", the particle of claim 23 produced by the process of claim 1 clearly does not contain any methylene chloride. This is not persuasive because by Appellants' definition, "essentially free" means less than 200, 100, 50, 20, or even 10 ppm methylene chloride (Specification at page 3, lines 24-31). As such, there is no requirement in the claims that absolutely no methylene chloride may be present in the claimed particles. Rather, the claims allow for 0 to 200 ppm methylene chloride. While it is acknowledged that Gillis *et al.* use a solvent system that comprises methylene chloride in the preparation of their coated particles, Gillis *et al.* teach that residual methylene chloride in the coated pellets is less than 600 ppm, preferably less than 300 ppm, and most preferably less than 250 ppm (page 4, lines 24-32). Further, in the preparation of coated pellets using a solvent system comprising methylene chloride, "[I]n order to reduce residual solvents levels in the drug coating layer...", the drug coated cores are ."...dried in a microwave vacuum apparatus at 150-400 mbar..." (page 10, lines 32-38). Further still, in preparing coated tablets, Gillis *et al.* teach that after microwave drying, the "dried coated cores" were warmed with dry air of about 50 ^{o}C and after application of a seal-coating, dried further by supplying dry air of 60 ^{o}C for 4 minutes (page 15, lines 20-31). It is a scientific fact that methylene chloride boils at 39.75 ^{o}C at atmospheric pressure. Appellants have presented no

factual evidence that treating the coated cores of Gillis *et al.* with a microwave generator for 1 hour at 25 kPa and 1 to 1.2 kW, followed by warming with dry air of about 50 °C, does not result in a residual methylene chloride level of less than 200 ppm as required by the instant claims.

Appellants assert that the lowest level of methylene chloride in the Gilis *et al.* product, "as noted by the Examiner", is <250 ppm. Appellants thus assert that using the microwave drying process disclosed in Gilis *et al.* could not achieve greater reductions in methylene chloride levels without burning or degrading the product itself. This argument is not persuasive because it is an allegation without factual support. As noted *supra*, Appellants have presented no factual evidence that carrying out the process disclosed in Gilis *et al.* does not result in coated particles having a residual methylene chloride content of less than 200 ppm as required by the instant claims. The levels disclosed in Gilis *et al*, *i.e.*, less than 250 ppm, include anything from 0 to 250 ppm, which clearly and unequivocally includes less than 200, 100, 50, 20, or even 10 ppm methylene chloride as encompassed by Appellants' definition of "essentially free".

Accordingly, in the absence of factual evidence to the contrary, carrying out the process as taught in Gilis *et al.* will inherently result in a coated particle "essentially free" of methylene chloride as recited in instant claim 23.

With regard to the 35 USC 103(a) rejection of claims 1-6, 15-16, 18-20, 22-23, and 43 as being unpatentable over Gilis *et al.* and Ishibashi *et al.* in view of Lynenskjold *et al.* and Nara *et al.*, Appellants' arguments have been fully and carefully considered but they are not deemed persuasive.

Appellants argue that the pharmaceutical dosage form disclosed in Gilis *et al.* is prepared using a solvent system comprising a mixture of dichloromethane and an alcohol and that Gilis *et al.* does not disclose a working solution containing both the drug and water as required by the present claims. Appellants further argue that Ishibashi *et al.* does not disclose both the drug and polymer in the same layer. Appellants further argue that while Lynenskjold *et al.* teach that the use of aqueous dispersions or solutions are preferred for coating solutions, and that alkanols (ethanol), ketones (acetone), and chlorinated hydrocarbons (methylene chloride) may also be used, none of the examples in Lynenskjold *et al.* disclose the use of any of these solvents with water. Appellants further argue that while Nara *et al.* disclose a drug core coated with a

composition comprising a water-insoluble substance, a swellable polymer, and optionally, a hydrophilic substance dissolved or dispersed in a solvent where the solvent can be water, an organic solvent, or mixtures thereof, Nara *et al.* does not disclose both the drug and polymer in the same layer.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In this regard, Appellants are picking and choosing specific teachings of the cited prior art in an attempt to show that the cited prior art does not teach or suggest the claimed invention. However, the only difference between the Gilis *et al.* reference and the claimed invention is the solvent system used to coat the core particles. Specifically, the pellets disclosed in Gilis *et al.* comprise: a) a central, rounded or spherical core having a diameter of about 710-1190 μM; b) a coating film of a **water-soluble polymer** and an **antifungal agent**; and c) a seal-coating polymer layer, characterized in that the residual solvent levels in said pellets is within limits set by the ICH, that is, the concentration of dichloromethane is less than 600 ppm, most preferably less than 250 ppm (page 4, lines 24-32). While the coating solution used in Gilis *et al.* comprises methylene chloride and ethanol, the instant claims require a coating solution comprising water and solvent selected from the group consisting of alcohol, acetone, and mixtures thereof. Ishibashi *et al.*, Lyneskjold *et al.*, and Nara *et al.* are provided as evidence that coating solutions comprising water, an alcohol, acetone, and mixtures thereof would have been *prima facie* obvious. That these references do not teach drug and polymer in the same layer is not pertinent to the present rejection because Gilis *et al.* teach this limitation of the instant claims.

Appellants allege that the Examiner has established no motivation to combine the references. In this regard, Appellants argue that there must be some suggestion or motivation to combine reference teachings or to modify the reference, there must be a reasonable expectation of success, and the prior art reference or references when properly combined must teach or suggest all of the claim limitations (citing MPEP 2143). Appellants further argue that a proposed modification cannot render the prior art unsatisfactory for its intended purpose and cannot change the principle operation of a reference (citing MPEP 2143.01). Firstly, the suggestion or

motivation to modify the process of Gilis *et al.* is explicitly found in Gilis *et al.* who expressly teach coated particles characterized in that the residual solvent levels in said pellets is within limits set by the ICH, that is, the concentration of dichloromethane is less than 600 ppm, most preferably less than 250 ppm (page 4, lines 24-32). Thus, one skilled in the art would recognize that using a solvent system that does not comprise methylene chloride would be effective for producing coated particles having a residual methylene chloride content of less than 250 ppm. Based on the teachings of Ishibashi *et al.*, Lyneskjold *et al.*, and Nara *et al.*, the skilled artisan would reasonably expect that a solvent system comprising water, alcohol, acetone, and mixtures thereof would be an effective solvent system for coating particles with a water-insoluble drug and water-soluble polymer. Regarding Gilis *et al.*, the principle operation of the Gilis *et al.* reference is to coat core particles with a water-insoluble antifungal agent and water-soluble polymer. Using a different coating solution than that expressly taught in Gilis *et al.* would not change this principle operation of the Gilis *et al.* reference.

Appellants argue that one of ordinary skill in the art would not substitute the water-containing solvent systems of Lynenskjold *et al.* or Nara *et al.* with those of Gilis *et al.* or Ishibashi *et al.*, because Gilis *et al.* and Ishibashi *et al.* provide no motivation to provide water in their coating systems for a very sparingly water-soluble active agent and hydrophobic substance, respectively. With respect to the coating solution used to coat the disclosed core particles, Gilis *et al.* teach that a drug coating solution is prepared by dissolving into a "suitable solvent system" appropriate amounts of an antifungal agent and a water-soluble polymer (page 9, lines 15-17). While Gilis *et al.* only disclose a solvent system comprising methylene chloride and ethanol, Ishibashi *et al.* discloses that solvent systems for coating particles should dissolve both the hydrophobic organic compound and water-soluble polymer (page 6, ¶ [0057]). The skilled artisan would recognize that a solvent system comprising water and ethanol/acetone would be effective to dissolve both a hydrophobic organic compound (ethanol/acetone) and water-soluble polymer (water). It would take no more than routine experimentation to test different solvent systems for coating core particles with a water-insoluble antifungal agent and water-soluble polymer.

Appellants argue that the process of the presently pending claims provides particles that have an increased solubility under dissolution conditions at pH 5.0, resulting in enhanced

bioavailability of the active ingredient. Referring to Table 5 at page 24 of the present specification, Appellants argue that the azole antifungal composition of the invention had a dissolution rate increase by 129% over the dissolution profile of the commercial product SPORANOX® under fasted conditions and an increase of 74% over the commercial product under fed conditions. The Examiner previously maintained that Appellants results are not persuasive of an unexpected result because Appellants do not describe how the itraconazole particles tested in the example at page 24 were prepared, nor how the SPORANOX® particles were prepared. Further, the Examiner previously maintained that Appellants' results are not commensurate in scope with the claims. In response, Appellants in the instant Appeal Brief point to the parent application of the presently pending application, U.S. Patent Application No. 09/933,032 and USP No. 6,663,897 to provide information regarding the process by which the itraconazole particles and SPORANOX® particles were produced. Appellants state that the itraconazole particulate compositions discussed in the present application are "consistent with" those described and disclosed at col. 6, lines 1-67 of the specification of the '897 patent.

Preparation of itraconazole particles of the invention and SPORANOX® particles are described in the instant Appeal Brief at pages 24-29. It is the position of the Examiner that not only are Appellants' results not commensurate in scope with the claims but further that Appellants' are not comparing particles formed by the claimed process to particles that differ *only* in the solvent system used to coat itraconazole particles. As discussed in the rejection of record, the only difference between the particles disclosed in Gilis *et al.* and the particles formed by the claimed process is the solvent system used to coat the particles. However, Appellants' particles contain the following ingredients:

Name of Ingredient	Percent	Quantity
Microcrystalline Cellulose Spheres (Celpheres)[1]	36.28	1,500 g
Micronized Itraconazole	18.86	780 g
Hydroxy Propyl Methyl Cellulose 5 cps	42.85	1,755 g
Titanium Dioxide USP	0.85	35.1 g
Hydrochloric Acid 37% NF/EP[2]	1.56	174.5 g
Alcohol SDAA Anhydrous[3]	0.0	28,970 g
Purified Water USP/EP[3]	0.0	3,264 g
Total	100.0	4,134.66 g

[1]CP 507 grade Celpheres ® are used
[2]Supplied as 37% Hydrochloric Acid and contributes 64.56 g of total solids
[3]Removed in the process

See page 24 of Appeal Brief. However, the SPORANOX® particles to which Appellants are comparing their particles do **not** contain titanium dioxide or hydrochloric acid. Further, in Appellants' preparation, particles are coated by using a spray rate of 15 grams to a final rate of 30 to 35 grams per minute. In contrast, the preparation of the SPORANOX® particles used a spray rate of 600 to 700 grams per minute and after delivery of 30% of the spraying solution, the delivery rate was increased to 700-800 grams per minute. Further still, the dried, coated SPORANOX® particles were subsequently seal-coated, while Appellants' particles were **not** seal-coated. Because of these significant differences in the preparation process of Appellants' particles and SPORANOX® particles, one cannot conclude that the differences in dissolution rates observed by Appellants were simply due to a change in solvent system, as suggested and motivated by the cited prior art, and not due to differences in spray rate, presence of titanium dioxide and/or hydrochloric acid, or presence of a seal-coating on the SPORANOX® particles.

To arrive at Appellants' claimed invention, one skilled in the art need **only** change the solvent system disclosed in the Gilis *et al.* reference from methylene chloride/ethanol to water/ethanol, water/acetone, or water/acetone/ethanol. As such, a proper comparison to the prior art would be: A) using Appellants' preparation method to prepare two particles, one using a solvent system of water/ethanol, water/acetone, or water/acetone/ethanol and the other a solvent system of methylene chloride/ethanol or B) using the preparation method for SPORANOX® particles to prepare two particles, one using a methylene chloride/ethanol solvent system of Gilis *et al.* and the other using a solvent system of water/ethanol, water/acetone, or water/acetone/ethanol. By additionally using different spray rates and not applying a seal-coating their particles, Appellants' preparation method is significantly different from the preparation method of SPORANOX® particles of the prior art and these differences are not recited in the instant claims. For example, the claims do not recite a spray flow rate and do not recite addition of titanium dioxide and/or hydrochloric acid. Dependent claim 22 recites coating the spheres of claim 1 with an external coating, but this embodiment was not tested by Appellants.

Accordingly, the finding by Appellants that particles "produced by the process of the presently pending application" dissolve more rapidly than the SPORANOX® particles is not evidence of an "unexpected result" that is commensurate in scope with the claims.

With regard to the 35 USC 103(a) rejection of claim 7 as being unpatentable over Gilis *et al.*, Ishibashi *et al*, Lynenskjold *et al.* and Nara *et al.* in view of Vladyka *et al*, Appellants' arguments have been fully and carefully considered but they are not deemed persuasive.

Appellants argue that the process of the presently pending claims is completely different from the process taught in Vladyka *et al.* and the process of Vladyka *et al.* is completely different from the references whose deficiencies it is meant to cure. In response, the Examiner respectfully submits that Vladyka *et al.* is cited only for its teaching that amorphous azole compounds were known in the art. Claim 7 recites use of an azole antifungal agent "in amorphous form". Such an amorphous form of azole antifungal agents was known in the art and therefore it would have been *prima facie* that this form of an azole antifungal compound could be predictably coated onto a core particle using the methods of the cited prior art. Appellants have presented no factual evidence that use of an amorphous form of an azole antifungal compound in their methods provides unexpected properties compared to other forms of azole antifungal compounds.

As noted *supra*, Appellants present no arguments traversing the 35 U.S.C. 103 rejection of claim 17 as being unpatentable over Gilis *et al.*, Ishibashi *et al.*, Lynenskjold *et al.*, and Nara *et al.* in view of Martindale or the Obviousness-Type Double Patenting rejection of claims 1-7, 15-20, 22-23, and 42 as being unpatentable over claims 1-17 of USP No. 6,663,897. Accordingly, the Examiner presumes that Appellants agree with these grounds of rejection.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/James D Anderson/

Primary Examiner, Art Unit 1614

Conferees:

/Ardin Marschel/

Supervisory Patent Examiner, Art Unit 1614

/Johann R. Richter/

Supervisory Patent Examiner, Art Unit 1616